

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application of: Pramod K. Srivastava

Confirmation No.: 8697

Serial No.: 09/657,722

Art Unit: 1642

Filed: September 8, 2000

Examiner: Christopher H. Yaen

For: PEPTIDES FROM STRESS
PROTEIN-PEPTIDE
COMPLEXES

Attorney Docket No: 8449-115-999

BRIEF ON APPEAL FEE TRANSMITTAL UNDER 37 C.F.R. § 41.20 (b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant's Brief on Appeal in connection with the above-entitled application is submitted herewith. The item(s) checked below apply:

- ☐ The Brief filing fee is \$340.00
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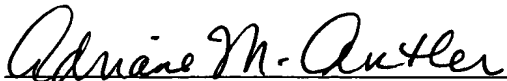
The brief filing fee is:

- ☒ Required.
- ☐ Not required. (Fee paid in prior appeal.)

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Respectfully submitted,

Date: December 6, 2004


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Enclosures



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BRIEF ON APPEAL

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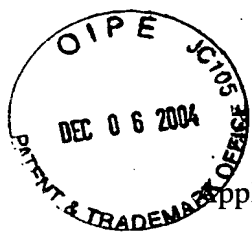
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FEDERAL STATUTES AND REGULATIONS

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OTHER REFERENCES

Liu <i>et al.</i> , 2002, “ <i>De novo</i> identification of the ever-elusive gp96-associated peptides,” Int’l Conf. on Heat Shock Proteins in Immune Response, Farmington, CT, Abstract, p.31 (October 6-9).....	7, 11
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Attorney Docket No: 8449-115-999

BRIEF ON APPEAL UNDER 35 U.S.C. § 134 AND 37 C.F.R. §§ 41.35 AND 41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal under 35 U.S.C. § 134 and 37 C.F.R. §§ 41.35 and 41.37 from a final rejection mailed March 8, 2004 of claims 19, 22-31, and 52-55 of the above-identified application. The Notice of Appeal was filed on June 4, 2004. Appellant submits this appeal brief accompanied by (1) a Petition for Extension of Time (in duplicate) for four (4) months from August 4, 2004 up to and including December 4, 2004, accompanied by the appropriate fee (in duplicate); and (2) a Brief on Appeal Fee Transmittal Sheet (in duplicate).

I. REAL PARTY IN INTEREST

Mount Sinai School of Medicine of New York University is the assignee of this application, and the real party in interest. The exclusive licensee of the application is Antigenics, Inc. An assignment transferring the right, title, and interest of inventor Pramod K. Srivastava in connection with priority application no. 08/315,892 (the above-identified application is a continuation of a continuation of a division of application no. 08/315,892) was recorded in the U.S. Patent and Trademark Office on June 26, 1995 at Reel 7524, Frame 0401.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings known to Appellant, Appellant's legal representative or assignee, which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 19, 22-31 and 52-55 are rejected.

Claims 1-18, 20-21 and 32-51 have been canceled without prejudice or disclaimer.

Claims 19, 22-31 and 52-55 are appealed.

IV. STATUS OF AMENDMENTS

All amendments have been entered. In the Advisory Action dated July 2, 2004, the Examiner stated that the Amendment Under 37 C.F.R. § 1.116 filed June 4, 2004 will be entered for purposes of appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to the observation that stress proteins associate noncovalently with (*i.e.*, chaperone) the antigenic peptides of cells, thus associating with a heterogeneous population of peptides inside a cell (see, *e.g.*, specification at page 5, lines 4-7). The presently claimed subject matter involved in the appeal, as defined in independent claim 19 (see Claims Appendix, *infra*), is a composition comprising a recovered population of peptides in admixture with a pharmaceutically acceptable non toxic carrier, wherein said recovered population of peptides is produced by a method comprising the steps of: (a) purifying a population of stress protein-peptide complexes from mammalian tumor cells, wherein the stress protein is noncovalently associated with the peptide in said complexes; (b) releasing the peptides from said population of complexes to produce a released population of peptides; and (c) recovering the released population of peptides (see, *e.g.*, specification at page 5, lines 4-7 and lines 19-27; page 6, lines 22-29; page 8, lines 9-18; page 12, line 20 to page 13, line 2; page 17, lines 5-12; and page 26, lines 13-16).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are presented for review in this appeal:

Firstly, claims 19, 22-31 and 52-55 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of proper written description.

Secondly, claim 19 stands rejected under 35 U.S.C. § 102 (b) as being anticipated by U.S. Patent No. 5,210,076 by Berliner *et al.* (“the ‘076 patent”).

VII. ARGUMENT

A. The Rejection of Claims 19, 22-31 and 52-55 Under 35 U.S.C. § 112, First Paragraph, For Lack of Written Description

1. Claims 19, 22-31 and 52-55

In the Office Action dated August 20, 2003, the Examiner maintains his rejection of claims 19, 22-31 and 52-55 and contends that they lack proper written description. As a basis of this rejection, the Examiner cites the “Revised Interim Written Description Guidelines Training Materials” (see, www.uspto.gov/web/offices/pac/writtendesc.pdf) which provides a synopsis and examples to determine whether the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied. The Examiner states that the written description guidelines describe “6 distinguishing characteristics that must be provide[sic] in order to fulfill the written description of a *product...*” (italics added). Aug. 20, 2003 Office Action at 3. Such characteristics include “partial structure, physical/chemical properties, functional characteristics, and known or disclosed correlation between structure and function.” *Id.* The Examiner alleges that the present invention only discloses the general structure of the HSP-peptide complex, but does not disclose or describe the characteristics listed above. The Examiner further alleges that “[t]here is a myriad of possible peptides that can be associated with the HSP-complex, of which the instant specification has not described.” The Examiner concludes by stating that “[a]bsent this information, one of skill in the art cannot readily make a determination of the contents of the claimed peptide composition, the structure of the composition, or any distinguishing characteristics associated with the composition, because the peptides isolated from the HSP complex differ and are not necessarily derived from the same protein.” Aug. 20, 2003 Office Action at 3-4. These contentions are essentially repeated in the final Office Action dated March 8, 2004.

With respect to the first issue on appeal, Appellant submits that the Examiner's rejection of claims 19, 22-31 and 52-55 for lack of proper written description is erroneous. To satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that at the time of filing, the inventor had possession of the claimed invention. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991) and *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404, 119 F.3d 1559 (Fed. Cir. 1997).

Appellant respectfully submits that the Examiner's rejection of the claims based on lack of proper written description is misplaced. Appellant submits that claims 19, 22-31 and 52-55 are product-by-process claims. By definition, a product-by-process claim is a product claim that defines the claimed product in terms of the process by which it is made, and is proper. The case law teaches that the mere fact that a claim to a composition is couched in terms of the process by which said composition is made, is not enough to render the claim objectionable. The Court of Customs and Patent Appeals (CCPA) has stated that "it is well established that product claims may include process steps to wholly or partially define the claimed product." *In re Luck*, 476 F.2d 650, 653, 177 U.S.P.Q. 523 (C.C.P.A. 1973). Further, the Patent and Trademark Office Board of Appeals held that "[i]t is proper to describe a composition or its component in terms of its method of preparation when more direct means of description are not available." *Ex parte Pantzer and Feier*, 176 U.S.P.Q. 141, 142 (Pat. & Tr. Office Bd. App. 1972). See also, *In re Thorpe*, where the Court of Appeals for the Federal Circuit stated that the "practice and governing law have developed in response to the need to enable an applicant to claim an otherwise patentable product that resists definition by other than the process by which it is made," *In re Thorpe*, 777 F.2d 695, 697, 227 U.S.P.Q. 964 (Fed. Cir. 1985). In *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 970 F.2d 834, 23 U.S.P.Q.2d 1481 (Fed. Cir. 1992), the Federal Circuit conducted a thorough review of U.S. Supreme Court, regional Circuit and CCPA case law addressing products claimed with process terms. The Federal Circuit came to the conclusion that product-by-process claims are an exception to the general rule requiring claims to define products in terms of structural characteristics, consistent with the Patent Office practice and CCPA decisions.

This principle has consistently been reaffirmed in subsequent Federal Circuit decisions relating to inventions pertaining to the chemical and biological arts. See, *e.g.*, *Fiers*

v. Revel, where the Federal Circuit recognized that “in addition to being claimable by structure or physical properties, a chemical material can be claimed by means of a process.” *Fiers v. Revel*, 984 F.2d 1164, 1169, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993), citing *Amgen v. Chugai*, 927 F.2d 1200, 1206, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Moreover, there is a distinction in the case law between product claims and product-by-process claims. See, *Ex parte Lyell*, 17 U.S.P.Q.2d 1548, 1552 (Bd. Pat. App. & Int. 1990), where the Board of Patent Appeals and Interferences recognized that a “product-by-process claim merely uses one statutory class of invention (*i.e.*, process limitations) to define or fingerprint another statutory class (*i.e.*, the product) which is not readily susceptible to definition solely by structure or physical characteristics,” citing *In re Thorpe*, 777 F.2d 695, 227 U.S.P.Q. 964 (Fed. Cir. 1985); *In re Brown*, 59 C.C.P.A.1036, 459 F.2d 531 (C.C.P.A. 1972); and *In re Pilkington*, 56 C.C.P.A. 1237, 411 F.2d 1345 (C.C.P.A. 1969).

A careful analysis of the appealed claims (claim 19, and dependent claims 22-31 and 52-55) reveals that they are indeed product-by-process claims, *i.e.*, they define the claimed product in terms of the process by which it is made. In particular, the preamble of claim 19 sets forth, “a composition,” by the process by which it is made, “a method comprising the steps of: purifying...; releasing...and recovering...”.

Appellant submits that one of the goals of the present invention is to capture the distinct antigenic profile from a given tumor for use as immunotherapy, and therefore product-by-process claims are the appropriate way to capture this aspect of the invention, since tumors are antigenically distinct and show antigenic diversity and heterogeneity (see, *e.g.*, page 3, lines 1-12 of the original specification as filed). Therefore, it is the very object of the present invention to circumvent the often daunting and impractical task of identifying individual immunogenic antigens of tumors from cancer patients (see, *e.g.*, page 3, lines 15-19 of the original specification as filed). As stated in the specification on page 3, line 33 to page 4, line 6:

Accordingly, it is an object of the instant invention to provide a novel method for therapeutically inhibiting proliferation of tumors in a mammal. The method described herein does not require the isolation and characterization of specific antigenic determinants, and accordingly provides a more rapid approach for making and using immunogenic compositions effective in inhibiting the proliferation of specific predetermined tumors in mammals.

To structurally identify each peptide within the large heterogeneous population of peptides that is associated with stress proteins inside a cell is an impractical task; purification and subsequent determination of the structural features of each individual peptide would have to be undertaken. The presently claimed invention avoids this very task. As such, Appellant has chosen to define the present invention by means of a product-by-process claim because it is the available practical means of defining the claimed invention, which is a *population* of peptides recovered from tumor cells (see, *e.g.*, claim 19 in the Appendix).

In view of the foregoing, the Examiner's final rejection of claims 19, 22-31 and 52-55 for lack of proper written description under 35 U.S.C. § 112, first paragraph, is erroneous and should be reversed.

B. The Rejection of Claim 19 Under 35 U.S.C. § 102 (b) as Anticipated by the '076 Patent

1. Claim 19

In the final Office Action dated March 8, 2004, the Examiner maintained the rejection of claim 19 under 35 U.S.C. § 102 (b) as being anticipated by U.S. Patent No. 5,210,076, issued May 11, 1993, by Berliner *et al.* ("the '076 patent"), as evidenced by Noessner *et al.*, 2002, *The Journal of Immunology* 169:5424-5432 ("Noessner"). The Examiner alleges that the '076 patent discloses a "tyrosinase protein wherein the said protein is found in [a] compound comprising a pharmaceutically acceptable carrier" (see, Aug. 20, 2003 Office Action at 4). Further, the Examiner alleges that as evidenced by Noessner, "tyrosinase is a peptide which can be associated with HSP70 protein thereby forming a complex, and because the claims are drawn to a product by process, and because the product being produced [is] already known, the process by which the product is made does not carry any patentable weight" (*Id.* at 5). The Examiner also contends that claim 19 is not so limited as to preclude a homogeneous mixture of peptides (*i.e.*, a mixture of a single protein) and a pharmaceutical carrier, and "because tyrosinases have been isolated and shown to complex with HSP-70, the claim is anticipated" (see, Mar. 8, 2004 Office Action at 4). Appellant respectfully submits that the '076 patent does not render claim 19 anticipated.

The '076 patent describes the use of melanin, its variants, analogs and derivatives, and other substances, including tyrosinase, to increase the concentration of melanin in the tissue of patients with certain neurodegenerative diseases which result in a loss

of melanin, such as Parkinson's disease, Alzheimer's disease, retinitis pigmentosa and dementia (the '076 patent at col. 1, lines 11-37). Tyrosinase is described as an enzyme that plays a key role in the synthesis of melanin and its derivatives (the '076 patent at col. 7, lines 61-62). Specifically, the '076 patent teaches that tyrosinase is an enzyme which catalyzes the reaction which converts precursors of melanin to melanin (the '076 patent, col. 1, lines 21-24). However, the '076 patent does not disclose or suggest the isolation of a population of peptides noncovalently associated with a stress protein in a mammalian tumor cell. The teaching of Noessner, a post-filing date reference, does not render the '076 patent anticipatory of the product claimed herein. Noessner describes results demonstrating that hsp70-peptide complexes purified from tyrosinase-positive but not tyrosinase-negative melanoma cells deliver the tyrosinase tumor associated antigen to immature dendritic cells for MHC class I-restricted T cell recognition (see Noessner at page 5425, col. 1, first full paragraph). Thus, Noessner teaches that a tyrosinase peptide is contained within the population of peptides complexed to hsp70 in a melanoma cell line.

With respect to the second issue on appeal, Appellant submits that the Examiner's rejection of claim 19 based on anticipation is erroneous. The legal standard for anticipation under 35 U.S.C. § 102 (b) is one of strict identity. A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377, 67 U.S.P.Q.2d 1664 (Fed. Cir. 2003); and *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943 (Fed. Cir. 1999). In other words, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991). See also, *Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989; "...identical invention must be shown in as complete detail as is contained in the patent claim").

However, the present invention relates to a *population* of peptides that are recovered from noncovalently complexed stress proteins. Moreover, the recovered population of peptides encompassed by the claims comprises a complex and heterogeneous mixture of peptides, *i.e.*, a plurality of different peptides. See Liu *et al.*, "De novo identification of the ever-elusive gp96-associated peptides," Int'l Conf. on Heat Shock

Proteins in Immune Response, Farmington, CT, October 6-9, 2002, Abstract, p. 31 (Reference GE in the revised Form PTO-1449 filed November 20, 2003). The '076 patent does not teach a population of peptides as set forth in the present claims. The '076 patent teaches tyrosinase. Such a protein is not the same as a *population* of peptides recovered from stress proteins.

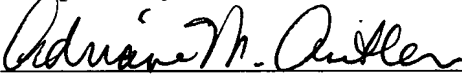
Accordingly, Appellant submits that the '076 patent fails to teach each and every element of the claimed invention. Thus, the '076 patent cannot anticipate the invention claimed herein. Appellant urges that the rejection of claim 19 under 35 U.S.C. § 102 (b) be reversed.

C. Conclusion

For all of the reasons set forth above, Appellant respectfully requests that all of the rejections of the claims on appeal be reversed.

Date: December 6, 2004

Respectfully submitted,

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VIII. CLAIMS APPENDIX
CLAIMS UNDER APPEAL
U.S. APPLICATION NO. 09/657,722
ATTORNEY DOCKET NO. 8449-115-999

19. (Previously Presented) A composition comprising a recovered population of peptides in admixture with a pharmaceutically acceptable non toxic carrier, wherein said recovered population of peptides is produced by a method comprising the steps of:

- (a) purifying a population of stress protein-peptide complexes from mammalian tumor cells; wherein the stress protein is non covalently associated with the peptide in said complexes;
- (b) releasing the peptides from said population of complexes to produce a released population of peptides; and
- (c) recovering the released population of peptides.

22. (Previously Presented) The composition of claim 19 further comprising a cytokine.

23. (Previously Presented) The composition of claim 22 wherein said cytokine is selected from the group consisting of IL-1 α , IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IFN α , IFN β , IFN γ , TNF α , TNF β , G-CSF, GM-CSF, and TGF- β .

24. (Previously Presented) The composition of claim 19 wherein the peptides are released from said population of complexes by a method comprising placing said population of complexes in the presence of adenosine triphosphate.

25. (Previously Presented) The composition of claim 19, wherein said mammalian tumor cells are human cells.

26. (Previously Presented) The composition of claim 19 wherein said mammalian tumor cells are from a tumor selected from the group consisting of melanocarcinoma, hepatocarcinoma, and renal cell carcinoma.

27. (Previously Presented) The composition of claim 19 wherein said tumor cells are from a metastasis.
28. (Previously Presented) The composition of claim 19, wherein said tumor cells have been proliferated *in vivo*.
29. (Previously Presented) The composition of claim 19, wherein said tumor cells have been proliferated *in vitro*.
30. (Previously Presented) The composition of claim 19, wherein the stress protein is a member of a stress protein family selected from the group consisting of hsp60, hsp70, and hsp90.
31. (Previously Presented) The composition of claim 19, wherein the stress protein is gp96.
52. (Previously Presented) The composition of claim 19, wherein the stress protein is hsp70.
53. (Previously Presented) The composition of claim 19, which further comprises a pharmaceutically acceptable carrier.
54. (Previously Presented) The composition of claim 19, further comprising an adjuvant.
55. (Previously Presented) The composition of claim 54, wherein the adjuvant is selected from the group consisting of a pluronic tri-block copolymer, muramyl dipeptide, detoxified endotoxin, saponin, QS-21, and liposome.

IX. EVIDENCE APPENDIX

Appellant submits herewith a copy of Liu *et al.*, “*De novo* identification of the ever-elusive gp96-associated peptides,” Int’l Conf. on Heat Shock Proteins in Immune Response, Farmington, CT, October 6-9, 2002, Abstract, p. 31 (reference GE), which was submitted with the Supplemental Information Disclosure Statement filed by Appellant on November 20, 2003, in response to the non-final Office Action dated August 20, 2003.

Pursuant to 37 C.F.R. § 41.37 (c)(1)(ix), Appellant submits that this reference has been entered by the Examiner and is relied upon by Appellant in the pending appeal. In a telephone conversation between Attorney for Appellant and Examiner Christopher H. Yaen on December 6, 2004, Examiner Yaen stated that reference GE was entered in the record on November 20, 2003.



III International Conference on
Heat Shock Proteins in Immune Response
FARMINGTON, CONNECTICUT, USA
OCTOBER 6-9, 2002



Abstract Book

ATTORNEY DOCKET NUMBER: 8449-115-999
SERIAL NUMBER: 09/657,722
REFERENCE: GE

***De novo* identification of the ever-elusive gp96-associated peptides**

Liu C*, Ewing N*, DeFilippo M*, Principato J*, Truneh A*, Zabrecky J*, *Srivastava P**

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Endoplasmic reticulum resident protein gp96 (or grp94) is a member of the heat shock proteins that are believed to be responsible for chaperoning antigenic peptides to T-cell surface, thus inducing an immune response. Both in vivo tumor rejection studies and in vitro antigen representation experiments support the notion that gp96 prepared under non-denaturing conditions has peptides associated non-covalently and the peptide repertoire is very diverse. However, efforts in demonstrating the diversity of peptides associated with gp96 using biochemical means have not been successful. This report presents the first study that confirms the diversity of peptides associated with gp96 and *de novo* identification of a significant number of peptides using mass spectrometry and protein database search.

Using a combination of guanidine hydrochloride and TFA, peptides can be efficiently dissociated from gp96. These peptides were separated from gp96 by membrane filtration and purified using a C18 reversed phase HPLC system. Peptide fractions were collected and analyzed by mass spectrometry. The mass spectrometry data were used to search protein database to identify the origin of these peptides. Mass spectrometry profiling of peptides from HPLC fractions detected several hundred peptides. Most of the peptides ranged in size between 700 Da and 3000 Da. Tandem mass spectrometry and protein database search identified more than 20 peptides with high confidence. A significant portion of the identified peptides exhibits high binding affinity to MHC I molecule. No obvious consensus in the amino acid sequence or biophysical properties can be established from these peptides.

X. RELATED PROCEEDINGS APPENDIX

None.